

In the Claims

The following amendments are made with respect to the claims in the International application PCT/EP2004/013861.

This listing of claims will replace all prior versions and listings of claims in this application.

- 1 (original). A liposome, wherein cholesterol (CH) and sphingomyelin (SM) are present in relation to the total molar lipid composition of the liposome at a molar ratio of 30 to 60 mol% and 5 to 20 mol%, respectively.
- 2 (currently amended). The liposome of claim 1, wherein SM is present in relation to the total molar lipid composition of the liposome at a molar ratio of 10 to 18 mol%, ~~in particular 12 to 16 mol%.~~
- 3 (currently amended). The liposome of claim 1[[ or 2]], wherein CH is present in relation to the total molar lipid composition of the liposome at a molar ratio of 40 to 56 mol%, ~~in particular 48 to 52 mol%.~~
- 4 (currently amended). The liposome of ~~one of claims 1 to 3~~ claim 1, wherein the remaining lipid of the liposome is selected from the group consisting of glycerides, glycerophospholipides, glycerophosphinolipids, glycerophosphonolipids, sulfolipids, sphingolipids, phospholipids, isoprenolides, steroids, stearines, steroles and carbohydrate containing lipids.
- 5 (original). The liposome of claim 4, wherein the phospholipid is selected from the group consisting of phosphatidylcholine (PC), phosphatidylserine (PS), and phosphatidylethanolamine (PE).
- 6 (original). The liposome of claim 5, wherein the PE is present in relation to the total molar lipid composition of the liposome at a molar ratio of 5 to 25 mol%.

- 7 (currently amended). The liposome of claim 5[[ or 6]], wherein the PC is present in relation to the total molar lipid composition of the liposome at a molar ratio of 15 to 40 mol%.
- 8 (currently amended). The liposome of ~~one of claims 1 to 7~~ claim 1, wherein the liposome has a diameter of between 50 to 200 nm, ~~preferably between 80 to 150 nm.~~
- 9 (currently amended). The liposome of ~~one of claim~~[[s]] 1[[ to 8]], wherein the SM is selected from the group consisting of SM derived from milk, SM derived from egg yolk, SM derived from brain, and synthetic SM.
- 10 (currently amended). The liposome of ~~one of claim~~[[s]] 1[[ to 9]], wherein the PE is selected from the group consisting of PE derived from egg; PE derived from heart; PE derived from liver; PE derived from plant; PE derived from bacteria; and synthetic PE, ~~in particular 1,2 diacyl sn-glycero-3-PE, 1 acyl 2 acyl sn-glycero-3-PE or 1,2 dilauroyl-sn-glycero-3-PE (DLPE).~~
- 11 (currently amended). The liposome of ~~one of claim~~[[s]] 1[[ to 10]], wherein a targeting moiety is attached to the liposome.
- 12 (currently amended). The liposome of claim 11, wherein the targeting moiety is selected from the group consisting of ~~a peptide or protein, in particular an antibody or fragment thereof, a single chain antibody or fragment thereof, a receptor ligand or fragment thereof, a carbohydrate; and a ligand~~ peptides and proteins; carbohydrates; and ligands.
- 13 (currently amended). The liposome of ~~one of claim~~ 11, in which the targeting moiety is selected from the group consisting of natural or synthetic receptor-binding peptides, ~~in particular integrin binding peptides such as RGD comprising peptides; growth factors, in particular VEGF, EGF, PDGF, TGF $\alpha$ , TGF $\beta$ , KGF, SDGF, FGF, IGF, HGF, NGF, BDNF, neurotrophine, BMF, bombesin, M-CSF, GM-CSF, thrombopoietin, erythropoietin, SCF, SDGF, oncostatin, PDEGF, endothelin; cytokines, in particular IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-14, IL-15, interferon  $\alpha$ ,  $\beta$  or  $\gamma$ , tumor necrosis factors such as TNF $\alpha$ , TNF $\beta$ ; chemokines, in~~

~~particular RANTES, MCAF, MIP-1 $\alpha$  or  $\beta$ , NAP,  $\beta$  thromboglobulin; peptide hormones such as SRH, SHH, STH, MRH, MSH, PRH, PIH, prolactin, LH-RH, FSH-RH, LH/ICSH, FSH, TRH, TSH, CRH, ACTH, angiotensin, kinine, histamine; steroid hormones, in particular estrogen, gestagen, androgen, glucocorticoid; mineral corticoids; or homologous or analogous thereof; vitamins, in particular folic acid; adhesion molecules, in particular lewis X, S-lewis X, LFA-1, MAC-1, VLA-4, PECAM, vitronectin, GMP-140, ICAM-1, VCAM-1, fibronectin, laminin, B7, CD28, CD40, CD40L and selectins; viral coatproteins; monosaccharides, in particular glucose, mannose; and oligosaccharides, in particular Man2, Man3, Man4, Man5, Man6, Man7, Man8, or Man9, lewis Y, sialyl lewis Y, and lectines.~~

14 (currently amended). The liposome of ~~one of claim~~[[s]] 11[[ to 13]], wherein the targeting moiety is attached to a spacer.

15 (currently amended). The liposome of claim 14, wherein the spacer has a length of between 1 and 10 nm, ~~preferably between 2.5 and 5 nm.~~

16 (currently amended). The liposome of ~~one of claims 11 to 15~~ claim 11, wherein the targeting moiety is attached to a lipid.

17 (currently amended). The liposome of claim 16, wherein the lipid is selected from the group consisting of N-caproylamine-PE, N-dodecylamine-PE, phosphatidylthioethanol, N-[4-(p-maleimidomethyl)cyclohexane-carboxamide]-PE (N-MCC-PE), N-[4-(p-maleimidophenyl)butyramide]-PE (N-MPB-PE), N-[3-(2-pyridyldithio)propionate]-PE (N-PDP-PE), N-succinyl-PE, N-glutaryl-PE, N-dodecanyl-PE, N-biotinyl-PE, N-biotinyl-Cap-PE, phosphatidyl-(ethylene glycol), PE-polyethylene glycol (PEG)-carboxylic acid, PE-PEG-maleimide, PE-PEG-PDP, PE-PEG-amine, PE-PEG-biotin, PE-PEG-HNS, dipalmitoyl-glycerolsuccinyl-lysine[[.]],  $\alpha$ -methoxy- $\omega$ -(1,2-dioctadecenoyloxy glyceryl) (DO), and  $\alpha$ -methoxy- $\omega$ -(1,2-ditetradecenoyloxy glyceryl) (DT).

18 (currently amended). The liposome of ~~one of claims 1 to 17~~ claim 1, wherein one or more drugs and/or diagnostics are ~~comprised~~ in the liposome.

19 (currently amended). The liposome of claim 18, wherein the drug is selected from the group consisting of analgetics, antirheumatics, anthelminthics, antiallergics, antianemics, antiarrhythmics, antibiotics, antiinfectives, antidemenics (nootropics), antidiabetics, antidotes, antiemetics, antivertiginosics,[[,]] antiepileptics, antihemorrhagics, antihypertotics, antihypotonics, anticoagulants, antimycotics, antitussiv agents, antiviral agents, beta-receptor and calcium channel antagonists, broncholytic and antiasthmatic agents, chemokines, cytokines, mitogens, cytostatics, cytotoxic agents and prodrugs thereof, dermatics, hypnotics and sedatives, immunosuppressants, immunostimulants, peptide or protein drugs, in particular hormones and physiological or pharmacological inhibitors of mitogens, chemokines, or cytokines or their respective prodrugs.

20 (currently amended). The liposome of claim 19, wherein the cytostatic[[s]] and cytotoxic drug[[s]] are selected from the group consisting of alkylating substances, anti-metabolites, antibiotics, epothilones, nuclear receptor agonists and antagonists, anti-androgenes, anti-estrogens, platinum compounds, hormones and antihormones, interferons and inhibitors of cell cycle-dependent protein kinases (CDKs), inhibitors of cyclooxygenases and/or lipoxygenases, biogeneic fatty acids and fatty acid derivatives, including prostanoids and leukotrienes, inhibitors of protein kinases, inhibitors of protein phosphatases, inhibitors of lipid kinases, platinum coordination complexes, ethyleneimenes, methylmelamines, trazines, vinca alkaloids, pyrimidine analogs, purine analogs, alkylsulfonates, folic acid analogs, anthracendiones, substituted urea, methylhydrazin derivatives, in particular acediasulfone, aclarubicine, ambazone, aminoglutethimide, L-asparaginase, azathioprine, bleomycin, busulfan, calcium folinate, carboplatin, carpecitabine, carmustine, celecoxib, chlorambucil, cis-platin, cladribine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin dapsone, daunorubicin, dibrompropamidine, diethylstilbestrole, docetaxel, doxorubicin, enediynes, epirubicin, epothilone B, epothilone D, estramucin phosphate, estrogen, ethinylestradiole, etoposide, flavopiridol, floxuridine, fludarabine, fluorouracil, fluoxymesterone, flutamide fosfestrol, furazolidone, gemcitabine, gonadotropin releasing hormone analog,

hexamethylmelamine, hydroxycarbamide, hydroxymethylnitrofurantoin, hydroxyprogesteronecaproat, hydroxyurea, idarubicin, idoxuridine, ifosfamide, interferon  $\alpha$ , irinotecan, leuprolide, lomustine, lurtotecan, mafenide sulfate olamide, mechlorethamine, medroxyprogesterone acetate, megastrolacetate, melphalan, mepacrine, mercaptopurine, methotrexate, metronidazole, mitomycin C, mitopodozide, mitotane, mitoxantrone, mithramycin, nalidixic acid, nifuratel, nifuroxazide, nifuralazine, nifurtimox, nimustine, ninorazole, nitrofurantoin, nitrogen mustards, oleomucin, oxolinic acid, pentamidine, pentostatin, phenazopyridine, phthalylsulfathiazole, pipobroman, prednimustine, prednisone, preussin, procarbazine, pyrimethamine, raltitrexed, rapamycin, rofecoxib, rosiglitazone, salazosulfapyridine, scriflavinium chloride, semustine streptozocine, sulfacarbamide, sulfacetamide, sulfachlopyridazine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfaethidole, sulfafurazole, sulfaguanidine, sulfaguanole, sulfamethizole, sulfamethoxazole, cotrimoxazole, sulfamethoxydiazine, sulfamethoxypyridazine, sulfamoxole, sulfanilamide, sulfaperin, sulfaphenazole, sulfathiazole, sulfisomidine, staurosporin, tamoxifen, taxol, teniposide, tertiposide, testolactone, testosteronepropionate, thioguanine, thiotepa, tinidazole, topotecan, triaziquone, treosulfan, trimethoprim, trofosfamide, UCN-01, vinblastine, vincristine, vindesine, vinblastine, vinorelbine, and zorubicin, or their respective derivatives or analogs thereof.

- 21 (currently amended). The liposome of claim 18, wherein the diagnostic is selected from the group consisting of [[an ]]electron dense molecules, [[a ]]paramagnetic molecules, [[a]] superparamagnetic molecules, [[a ]]radioactive molecules, [[a ]]non-radioactive isotopes, and [[a ]]fluorescent molecules.
- 22 (currently amended). The liposome of ~~one of claim~~ [[s]] 1[[ to 21]], wherein stabilizers, protectants, metal ion chelators, buffers and/or additives are ~~comprised~~ in the liposome.
- 23 (currently amended). The liposome of ~~one of claim~~ [[s]] 1[[ to 22]], which is dried; ~~preferably freeze dried~~.

- 24 (currently amended). A method for producing a liposome ~~of one of claims 1 to 23~~, in which SM, CH and remaining lipids(s) are mixed and wherein the method produces a liposome, wherein cholesterol (CH) and sphingomyelin (SM) are present in relation to the total molar lipid composition of the liposome at a molar ratio of 30 to 60 mol% and 5 to 20 mol%, respectively.
- 25 (original). The method according to claim 24 in which the remaining lipid is selected from PE and PC.
- 26 (currently amended). A pharmaceutical or diagnostic composition comprising ~~a liposome of one of claims 1 to 23 or produced according to the method of claim 24~~ a liposome, wherein cholesterol (CH) and sphingomyelin (SM) are present in relation to the total molar lipid composition of the liposome at a molar ratio of 30 to 60 mol% and 5 to 20 mol%, respectively, said composition further comprising a stabilizer[[s]], protectant[[s]], metal ion chelator[[s]], buffer[[s]] and/or additive[[s]].
- 27 (canceled).
- 28 (currently amended). The liposome of claim 22 ~~or 23, the pharmaceutical composition of claim 25 or the diagnostic composition of claim 27~~, wherein the stabilizers [[are]] is selected from the group consisting of  $\alpha$ -tocopherol, vitamin E [[or]] and carbohydrates, in particular glucose, sorbitol, sucrose, maltose, trehalose, lactose, cellubiose, raffinose, maltotriose, or dextran.
- 29 (currently amended). ~~Use of a liposome of one of claims 1 to 23 or a pharmaceutical composition of claim 26 or 28 for the production of a medicament for the therapy of~~ A method for the treatment of a proliferative disease[[s]], autoimmune disease[[s]], infectious disease[[s]], cardiovascular disease[[s]], rheumatoid disease[[s]], inflammatory disease[[s]] or any disease or condition, ~~which that~~ is associated with damage to or a permeability increase of the vasculature or the activation of endothelial cells wherein said method comprises administering to a patient in need of such treatment a liposome, wherein cholesterol (CH) and sphingomyelin (SM) are present in relation to

the total molar lipid composition of the liposome at a molar ratio of 30 to 60 mol% and 5 to 20 mol%, respectively.

- 30 (currently amended). The ~~[[use]]~~ method of claim 29, wherein the proliferative disease is selected from the group consisting of carcinomas of the gastrointestinal or colorectal tract, liver, pancreas, kidney, bladder, prostate, endometrium, ovary, testes, melanoma, dysplastic oral mucosa, invasive oral cancers, small cell and non-small cell lung carcinomas, hormone-dependent breast cancers, independent breast cancers, transitional and squamous cell cancers, neurological malignancies including neuroblastoma, gliomas, astrocytomas, osteosarcomas, soft tissue sarcomas, hemangioamas, endocrinological tumors, hematologic neoplasias including leukemias, lymphomas, and other myeloproliferative and lymphoproliferative diseases, carcinomas in situ, hyperplastic lesions, adenomas, fibromas, histiocytosis, chronic inflammatory proliferative diseases, vascular proliferative diseases and virus-induced proliferative diseases.
- 31 (currently amended). ~~[[Use]]~~ The method of ~~a diagnostic composition~~ of claim 27 for the diagnosis of a disease selected from the group of proliferative diseases, autoimmune diseases, infectious diseases, cardiovascular diseases, rheumatoid diseases, and inflammatory diseases.
- 32 (new). The liposome of claim 10, wherein the PE is 1,2-diacyl-sn-glycero-3-PE, 1-acyl-2-acyl-sn-glycero-3-PE or 1,2-dilauroyl-sn-glycero-3-PE (DLPE).
- 33 (new). The liposome, of claim 13, wherein the targeting moiety is selected from the group consisting of integrin binding peptides; VEGF; EGF; PDGF; TGF $\alpha$ ; TGF $\beta$ ; KGF; SDGF; FGF; IGF; HGF; NGF; BDNF; neurotrophine; BMF; bombesin; M-CSF; GM-CSF; thrombopoietin; erythropoietin; SCF; SDGF; oncostatin; PDEGF; endothelin; IL-1; IL-2; IL-3; IL-4; IL-5; IL-6; IL-7; IL-8; IL-9; IL-10; IL-12; IL-13; IL-14; IL-15; interferon  $\alpha$ ,  $\beta$  or  $\gamma$ ; tumor necrosis factors; RANTES, MCAF; MIP-1 $\alpha$  or  $\beta$ ; NAP;  $\beta$ -thromboglobulin; SRH; SIH; STH; MRH; MSH; PRH; PIH; prolactin; LH-RH; FSH-RH; LH/ICSH; FSH; TRH; TSH; CRH; ACTH; agiotensin; kinine; histamine; estrogene; gestagene; androgene; glucocorticoide; mineral corticoids; folic acid; lewis X; S-lewis X; LFA-1;

MAC-1; VLA-4; PECAM; vitronectin; GMP-140; ICAM-1; VCAM-1; fibronectin; laminin; B7; CD28; CD40; CD40L and selectins; glucose; mannose; Man2; Man3; Man4; Man5; Man6; Man7; Man8; Man9; lewis Y; sialyl lewis Y; and lectines.

34 (new). The liposome of claim 23, which is freeze dried.